Chemistry of Natural Compounds, Vol. 47, No. 6, January, 2012 [Russian original No. 6, November-December, 2011]

ALKYLATION OF *o*-CRESOL BY POLYPRENOLS

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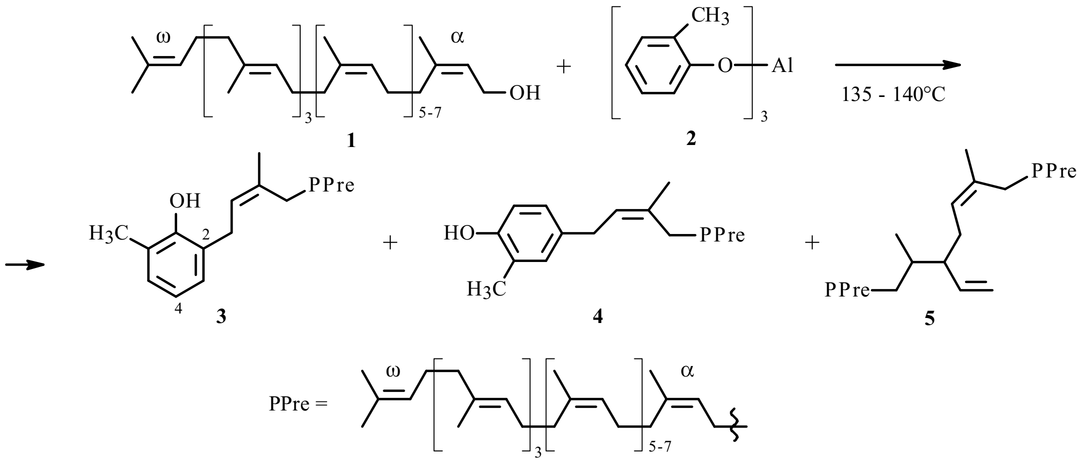
UDC 547.563.1+547.315+547.562/4'162

Aromatic compounds containing a prenyl moiety are found among biologically active compounds that regulate important metabolic processes [1–3]. In this respect prenylated phenol derivatives, which can be prepared using several methods, are certainly interesting. In our opinion, one of the most interesting preparation methods is direct Friedel–Crafts alkylation of phenols by polyprenols. This method was widely used recently even for catalytic asymmetric alkylation [4].

Herein we communicate results for the alkylation of *o*-cresol by polyprenols isolated from cotton leaves [5] and containing 10–12 isoprene units. The choice of *o*-cresol was due to the presence of two strong *o*- and *p*-orienting groups, i.e., methyl and hydroxyl, through the action of which the prenyl moiety could be directed into the *o*- and *p*-positions to form a mixture of polyprenol isomers. Furthermore, the expected compounds could exhibit new biological properties owing to the high biological activity [6].

Alkylation of cresol by polyprenols (**1**) was carried out according to the method developed for alkylation of phenol by geraniol in the presence of aluminum alkoxides [7, 8]. The Friedel–Crafts alkylation catalyst was aluminum *o*-cresolate (**2**). Aluminum phenolates are known to be *ortho*-selective catalysts of phenol alkylation by camphene, α-pinene, and dipentene [9]. Polyprenols C_{50}–C_{60} of 95% purity (according to PMR spectroscopy) that were isolated from *Gossypium hirsutum* L. leaves (cotton line L-4) grown on the experimental plot of the Institute of Genetics and NPO Biolog in Tashkent Oblast were used for alkylation of *o*-cresol. PMR spectra of the polyprenols exhibited singlets for methyl protons at 1.65 and 1.72 ppm that belonged to internal *trans*- and *cis*-isoprenoid units, respectively. Methyl protons of the chain ω- and α-terminuses resonated as singlets at 1.46 and 1.63 ppm, respectively. A broad triplet (J = 7.0 Hz) corresponding to methylene protons of the isoprenoid chain was observed at 2.01 and 2.13 ppm. A doublet characteristic of methylene protons of a hydroxyl appeared at weaker field (4.11 ppm). Olefinic protons of the chain middle (*cis*- and *trans*-) formed a broad multiplet at 5.16 ppm. The olefinic proton of the terminal unit resonated at 5.47 ppm (triplet).

Scheme 1 diagrams shows the alkylation of *o*-cresol by polyprenols C_{50}–C_{60}.



Scheme 1

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The principal products from *o*-cresol alkylation by polyprenols were 2-polyprenyl-6-methyl- (**3**) and 4-polyprenyl-6-methylphenols (**4**) and polymerization products of the polyprenols themselves (**5**). The reaction products were purified and separated by column chromatography over silica gel (Alfa Aesar 70/230 μ) with elution by hexane:Et_2O solvent systems of increasing polarity.

PMR spectra of **3** exhibited resonances for the prenyl part of the molecule with protons of methyls on the double bond at 1.64–1.81 ppm; methylenes, 2.05–2.09; and methines, 5.17 and 5.34. The *o*-cresol methyl resonated at 2.27 ppm; protons of the aromatic ring, at 6.80–7.04. The 3-H_{Ar} protons had chemical shift at 7.03 ppm as a doublet; 4-H_{Ar}, 7.00; 5-H_{Ar}, 6.81 as a doublet. Resonances of methylene protons of polyprenol α-units bonded to *o*-cresol were observed as doublets at 3.39 ppm. The *o*-cresol was determined to be mono-substituted by using the ratio of integrated intensities of the terpene and aromatic protons. The presence in the ^{13}C NMR spectrum of the resonance for polyprenol C-1 at 29.72 ppm indicated that the polyprenol was bonded to the *o*-position of *o*-cresol. The *ortho*-substitution of the phenol ring was confirmed by the presence in the IR spectrum of C–H bending vibrations at 739 cm^{-1}. Absorption bands of the polyprenol fragment were observed as stretching vibrations of the double bond at 1672 cm^{-1} and bending vibrations at 850 cm^{-1}.

Resonances of methyl protons of 4-polyprenol-6-methylphenol appeared in the PMR spectrum at 1.62–1.77 ppm as singlets; of methylenes, 2.05–2.09; of methines, 5.17–5.33. The resonance of the cresol methyl protons was observed at 2.26 ppm; of the aromatic protons, 6.70–7.15. Resonances of methylenes of polyprenol α-units bonded to the aromatic ring were observed as doublets at 3.29 ppm. The following proton resonances were seen in the aromatic part of the spectrum: 3-H_{Ar}, 6.89–6.96 ppm; 2-H_{Ar}, 6.70–6.73; 5-H_{Ar}, 7.15 as a 1H singlet. The hydroxyl proton resonated at relatively weak field (7.30 ppm, 1H, s).

Thus, alkylation of *o*-cresol by polyprenols in the presence of aluminum cresolate was investigated. Aluminum cresolate and polyprenols in an equimolar ratio at 135–140°C formed primarily *o*-polyprenylcresols, the content of which reached 41% with the fraction of the *p*-substituted isomer being 11%. Polymerization products (48%) consisted of 2–4 polyprenyl moieties and will be reported separately.

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